Changes in initiation of orienting gaze shifts after muscimol inactivation of the caudal fastigial nucleus in the cat

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1. The production of a goal-directed saccadic gaze shift involves the specification of movement amplitude and direction, and the decision to trigger the movement. Behavioural and neurophysiological data suggest that these two functions involve separate processes which may interact.

2. The medio-posterior cerebellar areas are classically assigned a major contribution to the control of saccade metrics, and previous cerebellar lesion studies have revealed marked dysmetria of visually triggered gaze shifts. In contrast, these studies did not provide evidence for a cerebellar role in saccadic initiation.

3. In the present study, we investigated in the head-unrestrained cat the deficits in both the initiation and the metrics control of saccadic gaze shifts following pharmacological inactivation of the caudal part of the fastigial nucleus (cFN).

4. After cFN inactivation, latencies for contraversive gaze shifts increased to about 137 ± 28% of normal, and latencies for ipsiversive gaze shifts decreased to about 84 ± 8% of normal. Similar changes in head movement latency were observed, such that the temporal coupling between eye and head components remained largely unaffected.

5. Contraversive gaze shifts were more hypometric as their latency increased. In contrast, the degree of hypermetria in ipsiversive gaze shifts was unrelated to latency.

6. These results suggest a functional role of the medio-posterior cerebellum in gaze shift initiation and in storing information about the target location and/or the desired gaze shift amplitude.

Saccadic eye movements represent an interesting model for the study of both the sensory-to-motor transformation processes and the triggering mechanisms that lead to movement initiation. Although our comprehension of the neural processes that determine the metrics (amplitude and direction) of a saccade has recently improved substantially (see Wurtz & Goldberg, 1989), much less is known about the processes involved in saccade initiation. Psychophysical studies have shown that saccade latency is related to various characteristics of the target stimulus (sensory modality, intensity, position in the sensory field, and spatial and temporal predictability), as well as to attention and state of gaze fixation (Hallett, 1986; Becker, 1989; Fischer & Weber, 1993). In contrast, the accuracy of a saccade is much less sensitive to these factors, with the exception of sensory modality, and in general, saccade accuracy is not related to saccade latency (Becker, 1989). The independent control of movement initiation and metrics has also been suggested by studies using double-step stimuli (Becker & Jürgens, 1979). When a target is suddenly displaced to a new location before movement onset, a saccade is triggered after a normal reaction time, but its amplitude depends on the time elapsed between the second target step and saccade onset. This ability to affect the amplitude of a saccade without changing its latency argues for the existence of separate neural processes involved in the control of movement metrics and movement initiation (Becker, 1989). Such a distinction is also supported by the neurophysiological studies that have identified, at different levels of the visuo-oculomotor pathways, distinct populations of neurons contributing either to attentive fixation ('fixation neurons' and 'omnipause neurons') or to the spatial encoding and/or triggering of an orienting saccade ('orientation' or 'pre-saccadic' neurons) (for review see Wurtz & Goldberg, 1989). Indeed, it is generally assumed that both inhibition of the former and activation of the latter conjointly allow saccadic generation by specifying, respectively, when and where the eyes move (Fuchs, Kaneko & Scudder, 1985; Fischer & Weber, 1993).

Nevertheless, the neural processes leading to saccade initiation ('when') may not be completely independent from the neural substrate of saccade metrics ('where') but somehow they may interact with each other. Such a link

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between the when and where mechanisms could be necessary to maintain accuracy by triggering the movement only when sufficient spatial information has been accumulated. For example, when the detection of a visual target is rendered difficult by the presence of distractors, saccade accuracy is improved by an increase in latency (Findlay, 1983; Ottes, Van Gisbergen & Eggermont, 1985). It is likely that this procrastination involves the inhibition by omnipause neurons of the pre-oculomotor saccadic burst neurons (Fuchs *et al.* 1985) and, at the level of the superior colliculus, the inhibition by fixation neurons of the orientation neurons (Munoz, Guitton & Pélisson, 1991; Munoz & Wurtz, 1993*a*). When a fixation stimulus is replaced by a peripheral target that calls for a saccade, these antagonistic neuronal populations may compete until the 'presaccadic burst' neuron population wins, thereby allowing the saccade to be launched. One fundamental problem that still needs to be solved, however, is the understanding of the dynamics and neural implementation of this competition.

Anatomical, electrophysiological and lesion studies have emphasized the role of the cerebellum in the control of saccade metrics, and delineated the medio-posterior areas (vermal lobules VI–VII and underlying caudal fastigial nucleus: cFN) as the critical territories involved. Indeed, these areas receive projections from many oculomotor and visual structures in the brainstem (cat and monkey: Carpenter & Batton, 1982; monkey: Noda, Sugita & Ikeda, 1990). Purkinje cells in vermal lobules VI and VII project to and monosynaptically inhibit cFN neurons (Noda *et al.* 1990), which in turn project to several oculomotor structures in the brainstem (Carpenter & Batton, 1982; Noda *et al.* 1990) and to the superior colliculus (e.g. Sugimoto, Mizuno & Uchida, 1982; May, Hartwich-Young, Nelson, Sparks & Porter, 1990). Saccade-related activities have been recorded in both vermal lobules VI–VII and cFN (cat: Gruart & Delgado-Garcia, 1994; monkey: Ohtsuka & Noda, 1991*b*; Fuchs, Robinson & Straube, 1993; Ohtsuka & Noda, 1995), and low-intensity electrical microstimulation of either lobules VI–VII or the cFN evokes saccadic eye movements (Cohen, Goto, Shanzer & Weiss, 1965; Fujikado & Noda, 1987; Noda, Murakami, Yamada, Tamaki & Aso, 1988). Finally, any acute dysfunction of the FN involving its caudal part leads to dysmetric saccades in the head-fixed monkey (Vilis & Hore, 1981; Ohtsuka & Noda, 1991*a*; Robinson, Straube & Fuchs, 1993; Ohtsuka, Sato & Noda, 1994). This dysmetria, which resembles that reported in human cerebellar patients (Lewis & Zee, 1993), has been interpreted as a deficient modulatory action normally exerted by cFN during movement execution on the brainstem saccadic pulse generator ('movement execution' hypothesis) (Ohtsuka & Noda, 1991*b*; Robinson *et al.* 1993). Recently, we investigated in the head-unrestrained cat the deficits of saccadic shifts of gaze (eye + head) after cFN inactivation, and the type of gaze dysmetria observed led us to propose that the cFN also contributes to the processes which specify movement metrics during the period that precedes movement onset ('movement specification' hypothesis) (Goffart & Pélisson, 1994).

By comparison, a cerebellar role in the initiation of saccadic eye movements is, at present, only conjectural. On one hand, the fact that cFN neurons discharge a burst of activity preceding contraversive saccades (Ohtsuka & Noda, 1991*b*; Fuchs *et al.* 1993; Gruart & Delgado-Garcia, 1994) and that electrical stimulation can evoke contraversive saccades (Cohen *et al.* 1965; Noda *et al.* 1988) suggests a possible cFN involvement in saccade initiation. This would be compatible with projections to the superior colliculi and to the controlateral nucleus raphe pontis containing omnipause neurons (Langer & Kaneko, 1984; Noda *et al.* 1990). On the other hand, there has been no report of consistent modifications in saccade latency after temporary cerebellar lesions. We are aware of only two studies that measured saccade latency after inactivation of the fastigial nucleus by cooling probes (Vilis & Hore, 1981) or by muscimol injection (Robinson *et al.* 1993): the first mentioned no change of saccadic latency while the other reported inconsistent changes for the two monkeys studied. If, according to the 'movement specification' hypothesis, cFN controls processes that unfold during the preparatory period, changes in latency may occur together with dysmetria. In contrast, the 'movement execution' hypothesis by definition excludes the possibility of any change in saccade latency.

We have therefore investigated the latency of saccadic gaze shifts produced by the head-unrestrained cat after unilateral inactivation of the cFN, under the same conditions as in our previous study on gaze dysmetria (Goffart & Pélisson, 1994). We chose to record the gaze shifts that consist in co-ordinated eye–head movements elicited by the presentation of a food target as they belong to the cat's natural repertoire, and because head-unrestrained gaze shifts have been proposed to be controlled by central mechanisms similar to those proposed for saccadic eye movements performed with the head restrained (see Guitton, 1992, for review). We show that the latency of visually triggered gaze shifts consistently changes following injection of muscimol in the cFN. Moreover, these latency modifications can interact with muscimol-induced gaze dysmetria. A preliminary report of the results presented in this paper has been previously published in abstract form (Pélisson & Goffart, 1996).

METHODS

Animal preparation

Experiments were carried out in five cats prepared for the chronic recording of orienting movements and pharmacological local injections. Cats were manipulated in accordance with the guidelines of the French Ministry of Agriculture (87/848) and of the European Community (86/609/EEC). The animals were closely monitored throughout all experimental phases and after each muscimol injection until all behavioural deficits (the deficits to be reported in this paper as well as slight postural instabilities related

to a lateropulsion of the body towards the injected side) had vanished. Each animal was prepared in a single surgical procedure performed under general anaesthesia (sodium pentobarbitone, 30 mg kg^{-1} I.P. for induction and 1–3 mg kg^{-1} h^{-1} I.V. during surgery) and aseptic conditions. Two three-turn coils made of Teflon-coated stainless-steel wire (Cooner Wire, Chatsworth CA, USA; o.d., 0·3 mm) were implanted. One was sutured to the sclera of the right eye, the other was fixed to the skull with acrylic cement, and the leads (after passing under the skin the eye coil leads to the top of the head) were soldered to two connectors cemented to the skull. These two coils permitted us to record the position of gaze and head, respectively, by the search-coil-in-magnetic-field technique (Robinson, 1963). A trephine hole was made in the occipital bone to allow access to both deep cerebellar medial nuclei, and the dura mater was left intact. A 10 mm recording chamber, tilted 20 deg backward from the frontal plane, was positioned stereotaxically around the hole by aiming its centre at a location situated on the mid-line between the fastigial nuclei. After cleaning, a drop (0·3 ml) of saline solution containing framycetin sulphate (10 mg ml^{-1}) local antibiotic was added before sealing the chamber with a plastic cap. Finally, a U-shaped plastic piece was fixed to the head with cement and screws. This lightweight head-restraining piece, with transverse holes drilled in it, permitted the painless restrainment of the animal's head during some of the experimental phases (see below).

During the week after surgery, the animals were treated with sodium amoxicillin antibiotic (50 mg kg^{-1} (24 h)$^{-1}$ I.M.) and given analgesic (paracetamol) as needed, and the right eye treated bi-daily with an antiseptic cethexonium eyewash. Thereafter, the chamber and the wound at the edge of the head implant were regularly inspected and cleaned with sterile saline and antibiotics (0·3 ml of framycetin sulphate, 10 mg ml^{-1}), respectively, and with betadine and framycetin ointment. There was no effect of the head implant or eye coil on the welfare of the animals, as judged by regular and careful observations of their general behaviour and of their eyes (motility, lid aperture and pupil size were identical in the operated and the unoperated eye).

Experimental set-ups and animal training

The animals were deprived of food overnight before each experimental test. During testing, each cat was placed in a hammock, which gently restrained the body without restricting the natural movements of the head. The hammock was placed inside a 1 m diameter coil frame (CNC Engineering) with the head positioned at the centre of the frame. The visual target was a spoon filled with a food purée, fitted with two infrared diodes that allowed the continuous recording of its position (Urquizar & Pélisson, 1992). Cats were trained to orient their gaze towards the target upon its sudden presentation and were rewarded directly from the spoon after each successful orienting response. Recording sessions lasted between 1 and 2 h depending on the animal's appetite. They were terminated when the animal's motivation declined as indicated by a slowing of its gaze saccades or the absence of orienting response. The remainder of the food was offered to the animal when it had been returned to its cage to ensure that the animal received the same daily allowance as on the non-testing days.

Two experimental set-ups were used for target presentation. In the first one ('screen set-up'), the target was presented randomly to either side (up, down, left or right edge) of a planar, opaque screen situated 41 cm in front of the animal. Screens of different widths were used to provide target eccentricities along the azimuth of ±7, ±15, ±19, ±27 or ±35 deg with respect to the body mid-sagittal plane. A second target presentation apparatus used a semi-cylindrical (radius, 41 cm) opaque screen centred on the animal's head ('semi-cylindrical set-up'). The target could protrude through one of nine holes made in the panel, located at cat's eye level and at eccentricities of 0, ±12, ±24, ±36 or ±48 deg with respect to the mid-sagittal plane. In both set-ups, the animal was rewarded directly from the food target after eye- and head-orienting movements were completed. Although a fixation stimulus was usually present, the animals had not been specifically reinforced for accurately fixating before target presentation. Thus, the resulting variability of initial gaze position, combined with the different target locations used, permitted us to test a continuous range of target retinal eccentricities (see Figs 4 and 8). The second consequence was that the animal incidentally generated a spontaneous gaze shift at the time the target was presented, but this kind of movements was excluded from analysis (see below). There was no constraint regarding either speed or accuracy of the orienting gaze response, and the reward was suspended only when the animal produced anticipatory responses or no response at all.

An experiment consisted of a series of 2 s trials. Each trial was initiated and data acquisition started when the animal looked close to the centre position of the screen: the target, which was held behind the screen by the experimenter, was then presented and the animal had about 1·5 s to initiate and complete its orienting response. In most of the trials (90%), the ambient lights were shut off upon gaze shift onset to eliminate any visual feedback until the end of the trial. Each 'post-inactivation' recording session was performed within 20–120 min following muscimol injection, a period much shorter than the total duration of observed deficits (at least 4 h), also no sign of recovery could be noted during any recording session. Post-inactivation sessions were separated each other by at least three days. A control ('pre-inactivation') session was performed on the day preceding each pharmacological session.

Muscimol injections

The injection sites were first determined on a stereotaxical basis. In addition, for each experiment, we carefully noted whether the injection induced other deficits than those affecting visually triggered gaze shifts (e.g. spontaneous nystagmus, postural or vegetative deficits). It rapidly became clear that these side-effects were not observed when inactivation was restricted to the cFN and when present, they provided reliable information about any errors in the placement of the cannula. In cat H, stereotaxical data were confirmed electrophysiologically by recording from characteristic saccade-related neurons in the alert, head-fixed animal. The head of the animal was gently immobilized by attaching the head-restraining piece to the hammock frame. The recording chamber was opened and the dura covered with a drop of local anaesthetic (lidocaine/lignocaine, 5%) for 2 min; then the dura was cleaned and pierced with the tip of a hypodermic needle, and finally the electrode was lowered.

The same preparatory procedure was used before each muscimol injection. A Hamilton syringe filled with a saline solution of muscimol (1 $\mu g\ \mu l^{-1}$, Sigma), was connected to a thin cannula (230 μm o.d. bevelled tip) through a catheter. This cannula was lowered through the chamber and aimed at the injection site, using standard techniques (x–y positioner and motor-controlled hydraulic microdrive from TrentWells, Coulterville, CA, USA). A small volume of muscimol (0·3 μl) was injected by small pulses of 0·05 μl over a total period of 5 min. The cannula remained in place for 5 min before withdrawing.

To allow histological reconstruction of the injection sites, electrolytic marks were made at the end of the experimental series

(6–8 months post-implantation) by passing cathodal current through an electrode (30 μA for 20 s, an intensity that never induced any behavioural response, in the animals that were subsequently tested in another behavioural study and 500 μA for 20 s in the other animals that were deeply anaesthetized just before being killed). All animals received an overdose of anaesthetic and were perfused transcardially with saline, followed by 10% formalin. Standard techniques were used to prepare 60 μm slices on a freezing microtome and to reconstruct electrolytical lesions and injection sites. All sites of muscimol injection were located inside the caudal part of fastigial nucleus, as illustrated by the examples shown in Fig. 1. Also, based on the extent of the muscimol diffusion that can be inferred from measurements in the rat (1·7 mm maximum diffusion radius for 1 μl of 1 μg μl^{-1}; Martin, 1991), and on the specificity of the deficits reported below compared with those induced when muscimol is injected 2 mm away (L. Goffart and D. Pélisson, unpublished data), we believe that inactivated neurons lay within 1 mm of our injection sites. The contour of this estimated diffusion zone is illustrated in Fig. 1 for two reconstructed injections, showing that a reasonable amount of tissue within the cFN was presumably inactivated. Finally, test experiments performed in one animal (H) revealed that quantitative, but not qualitative, differences in deficits were observed when injecting within 1 mm of these cFN sites, which suggests that either muscimol is unlikely to spread out from the cFN or that nearby structures do not play a role in controlling the parameters investigated here.

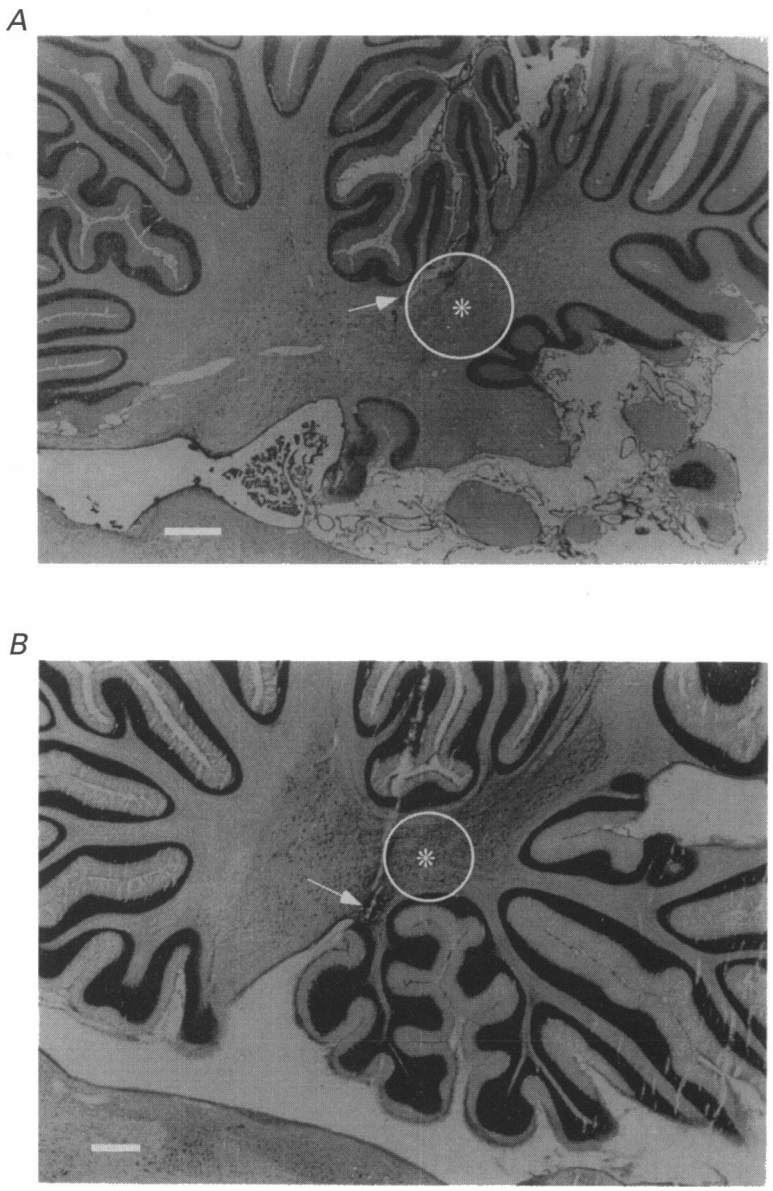

Figure 1. Histological reconstruction of injection sites in cFN

Parasagittal sections through the cerebellum showing a marking lesion (indicated by the arrows), and the sites of muscimol injection (*) reconstructed from the electrolytical lesion (*A*, cat G; *B*, cat H). The circles are estimations of the radius of muscimol inactivation. The rostral borders are indicated by the 1 mm scale bars.

Recording and calibration of orienting movements

Signals from eye and head coils were linearized and scaled on-line by a custom-written computer program, providing four signals proportional to the horizontal and vertical positions of gaze (eye in space) and head. The calibration of the coil signals was achieved in a two-step procedure. First, before implantation, we used Fick gimbals to rotate each eye and head coil about known angles in the horizontal and vertical planes and measured the corresponding voltages. These measurements allowed us to find the optimal values of gain and offset parameters for the linearization algorithm. Second, we checked, and if necessary corrected, these calibration parameters *in vivo* by presenting the animal with an attractive food target at known positions in the visual field. The estimated precision of measurement of gaze and head positions is within $\pm 0{\cdot}5$ deg.

Horizontal and vertical signals of gaze, head and target positions were sampled (frequency, 500 Hz) by blocks of 2 s (see above), displayed on-line and stored to disk on a PC microcomputer with the Experimenter's WorkBench software (DataWave).

Data analysis

The analyses presented in this paper were performed on gaze shifts elicited by targets presented along the azimuth. Only responses with very long latencies (> 1200 ms) and spontaneous movements generated close to the time of target presentation were rejected from analysis. Depending on the sessions, these responses represented 1–5% of the total sample. We used an 80 ms latency threshold to reject spontaneous gaze shifts, a value corresponding to the minimum visuomotor delay estimated from both our previous experience and from the sum of visual and motor delays of collicular output neurons (57 ms average visual latency (Guitton & Munoz, 1991) and 20 ms motor delay (Munoz *et al.* 1991)). Calculations were performed off-line with PC-compatible programs developed in our laboratory. Gaze and head position signals were digitally filtered (FIR filter, 70 Hz cut-off frequency) and differentiated. The onset and termination of gaze shifts and of head movements were detected based on a velocity threshold (30 deg s^{-1}). The results of this automatic process were checked by displaying each trial. Spatial and temporal parameters of eye, head and gaze movements were then automatically extracted from the detected movements and further processed by spreadsheet and statistical programs. The main parameters analysed in the present paper are gaze latency, head latency and the horizontal amplitude of gaze shift. Gaze latency was defined as the time between target presentation and gaze shift onset, and head latency as the time between target presentation and head movement onset. Target presentation in the first set-up was defined as the time at which the target crossed the screen edge, and this event was detected by a threshold on the target position signal. In the second set-up, target presentation was defined as the time the target entered one of the holes in the semi-circular screen as signalled on-line by an infra-red beam. Linear regression analyses and statistical comparisons were performed by a PC-based commercial package (Statistica by StatSoft).

RESULTS

The data reported here concern twelve injections made in five different animals (E, F, G, H and I). We will first present data demonstrating that muscimol injection in the cFN leads to changes in gaze and head latency. Then, the extent to which modifications in gaze shift initiation interact with gaze dysmetria will be reported.

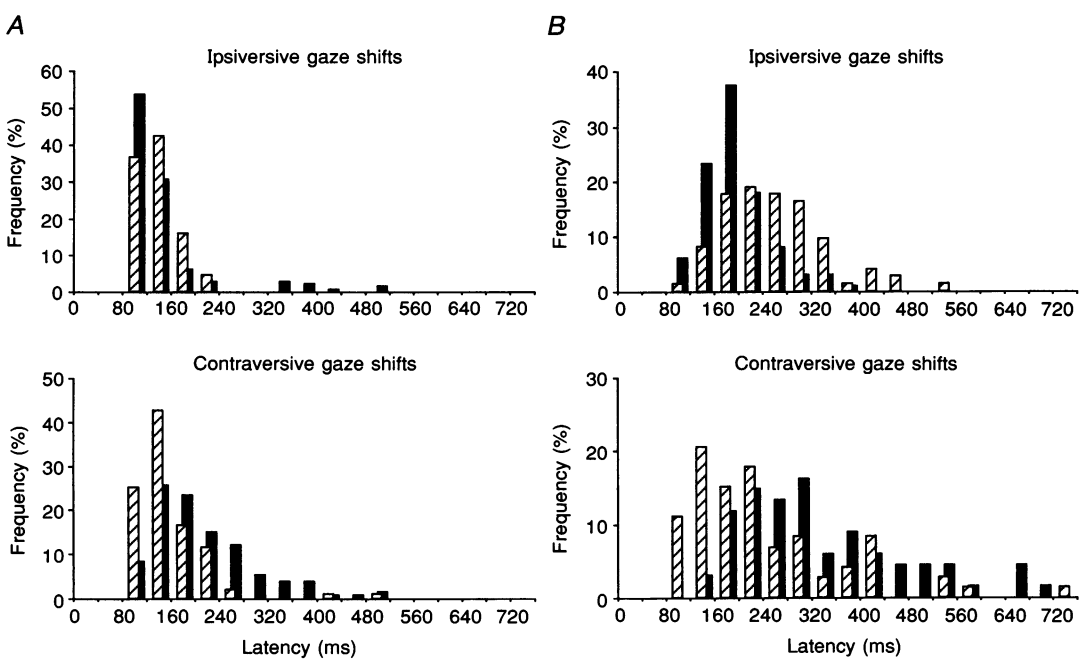

Figure 2. Effect of muscimol injection in the left cFN on the frequency distribution of gaze latencies

Responses were recorded before (▨) and after muscimol injection (■), respectively. Gaze shifts of cat G (*A*, injection G1) were obtained with the screen set-up, whereas those produced by cat I (*B*, injection I2) were obtained with the semi-cylindrical set-up. Latencies of movements directed towards and away from the injected side are represented in the upper and lower panels, respectively.

Latency of gaze and head movements

Unilateral inactivation of cFN leads to consistent changes in the latency of visually triggered gaze shifts. In Fig. 2, the frequency distribution of gaze latencies is illustrated for injections made in two different cats. Figure 2*A* shows the latencies of movements that were recorded in cat G using the screen set-up, before (▨) and after (■) an injection in the left cFN (injection G1). Figure 2*B* corresponds to cat I for which the semi-cylindrical set-up was used and injection made in the left cFN (injection I2). Leftward movements are reported in the upper panels of the figure, rightward ones in the lower panels. Regarding the control values, a single peaked distribution is observed for both movement directions and experimental set-ups. The larger latency range for cat I (87–731 ms), compared with cat G (83–498 ms), can be explained by the greater target position uncertainty with the semi-cylindrical set-up. For both set-ups, muscimol injection in the cFN led to a decrease in the latencies of leftward (ipsiversive) responses and an increase in the latencies of rightward (contraversive) ones.

This reduced latency of ipsiversive movements and increased latency of contraversive ones has been confirmed by comparing the median latency between the control and the pharmacological sessions. Figure 3 summarizes the data from all twelve experiments. Each hatched and filled column represents the median latency (upper quartile values shown as bars) of movements recorded before and after muscimol injection in the cFN, respectively. Overall, this figure shows a marked increase in both the median (mean increase, 71 ms) and the upper quartile value of gaze latency for responses directed away from the inactivated cFN (Fig. 3*B*). Changes in median latency with respect to the control responses were tested for each of the twelve experiments (Mann–Whitney *U* test). The increase in the median latency of contraversive responses is statistically significant for eleven experiments. In contrast, the latency of ipsiversive responses decreases (mean change, −28 ms) with respect to control values (Fig. 3*A*). Although this effect is less pronounced than that for contraversive responses, it is statistically significant in nine experiments. Similar observations were made regarding the latency of head movements. For contraversive responses, an increased head movement latency is statistically significant for ten experiments (Mann–Whitney *U* test) whereas for ipsiversive head movements, latencies are significantly reduced for seven experiments. In addition, these modifications in head latency (mean, 62 and −18 ms for contraversive and ipsiversive responses, respectively) are, on average, similar to changes in the latency of the corresponding gaze shifts (71 and −28 ms, respectively). These effects correspond to relative modifications of 137 ± 28 and $84 \pm 8\%$ for contraversive and ipsiversive gaze latency, respectively, and 134 ± 29 and $80 \pm 13\%$ for contraversive and ipsiversive head latency, respectively. Note that these changes are not an artefact associated with the use of a velocity threshold (Methods), since the recorded trajectory of pre- and post-inactivation movements superimpose well until long after this criterion is reached.

Interaction between latency and metrics of gaze shifts

We have previously shown that unilateral muscimol injection in the cFN leads to a hypermetria of ipsiversive gaze shifts and a hypometria of contraversive ones, respectively characterized by a constant bias and an error proportional to the required gaze shift amplitude (Goffart & Pélisson, 1994). Indeed, ipsilateral hypermetria could be described by a shift in the relationship between horizontal

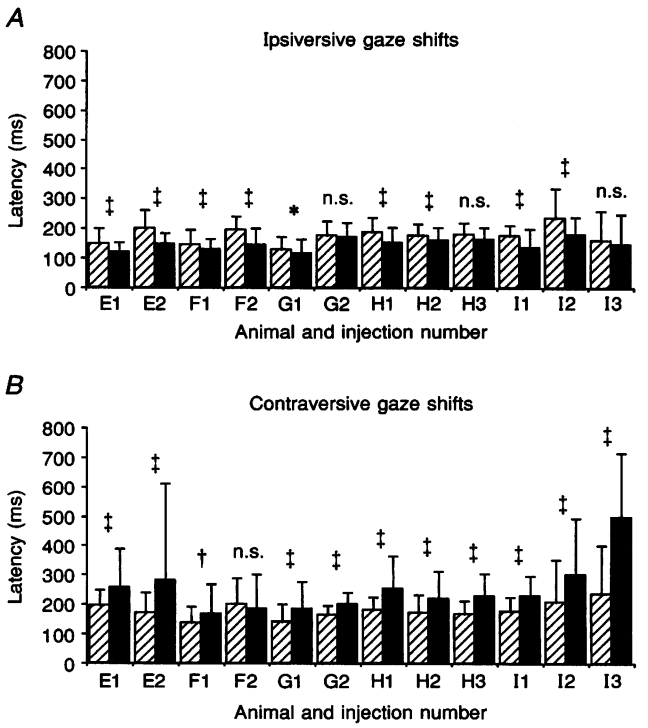

Figure 3. Effect of muscimol injection in the cFN on the latency of gaze shifts

Median latencies of gaze shifts recorded during the control session are represented by ▨, those after muscimol injection in the cFN by ■. The error bar represents the upper quartile value. Gaze shifts directed towards and away from the injected side are reported in *A* and *B*, respectively. Gaze latencies observed after each muscimol injection have been compared with corresponding control data using the Mann–Whitney *U* test (n.s., difference not statistically significant; * $P < 0{\cdot}05$; † $P < 0{\cdot}01$; ‡ $P < 0{\cdot}001$). Control and muscimol data from injections I2 and I3 were obtained with the semi-cylindrical set-up.

gaze displacement and horizontal retinal error (target eccentricity relative to gaze) whereas contralateral hypometria was associated with a reduced slope of this relationship.

To test whether the changes in latency reported above were associated with any modification in gaze metrics, we compared, separately for ipsiversive and contraversive gaze shifts, the relationship between horizontal retinal error and horizontal gaze amplitude for short-latency and longer latency responses. Gaze displacements were classified according to gaze median latency: gaze shifts with a latency smaller than the median were defined as short-latency movements and the others were considered as longer latency movements. The relationship between horizontal retinal error and horizontal gaze amplitude is illustrated in Fig. 4 for these two subsets of gaze shifts recorded after injections G1 (panels *A* and *B*) and I2 (panels *C* and *D*). As already reported, these relationships markedly differ from the control data, either in the *y*-intercept for ipsiversive displacements or in the slope for contraversive ones. Now we calculate, for each movement direction, the post-

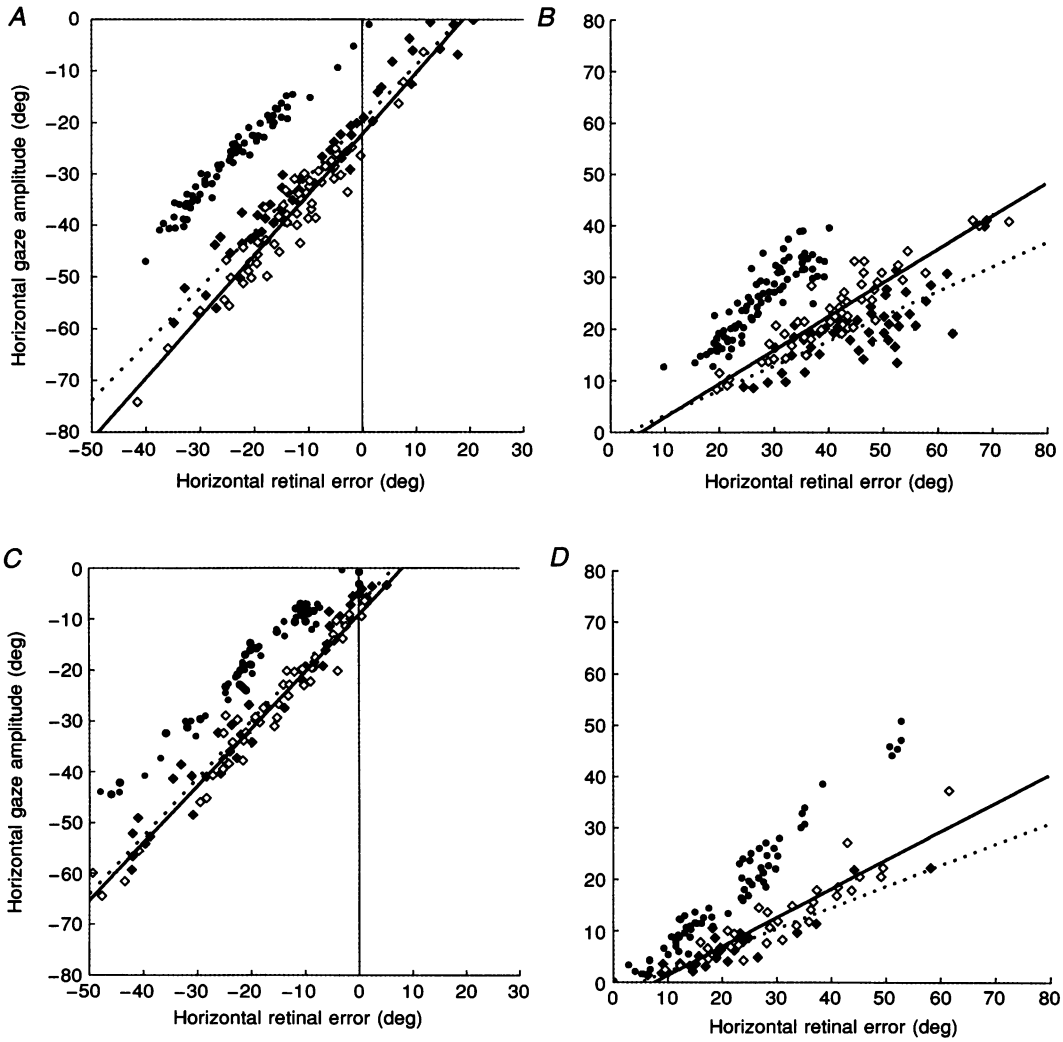

Figure 4. Latency and relationship between horizontal retinal error and horizontal gaze amplitude after muscimol injection in the left cFN

A and *B*, injection G1; *C* and *D*, injection I2. The relationships between horizontal retinal error (*x*-axis) and horizontal gaze amplitude (*y*-axis) of ipsiversive and contraversive gaze shifts are reported in the left- (*A* and *C*) and right-hand panels (*B* and *D*), respectively. Filled circles correspond to control movements recorded before muscimol injection, and the diamonds correspond to the muscimol data. The metrics of short-latency (◇, latency < median) and longer latency (◆, latency > median) gaze shifts is quantified by the continuous and dashed regression lines, respectively. Equations of the short- and longer latency regression lines are: in *A* (median latency, 118 ms) $y = 1{\cdot}18x - 22{\cdot}17$ ($r^2 = 0{\cdot}91$, $P < 0{\cdot}001$) and $y = 1{\cdot}08x - 19{\cdot}62$ ($r^2 = 0{\cdot}95$, $P < 0{\cdot}001$); in *B* (median latency, 184 ms): $y = 0{\cdot}65x - 3{\cdot}67$ ($r^2 = 0{\cdot}65$, $P < 0{\cdot}001$) and $y = 0{\cdot}48x - 1{\cdot}56$ ($r^2 = 0{\cdot}58$, $P < 0{\cdot}001$); in *C* (median latency, 181 ms): $y = 1{\cdot}11x - 9{\cdot}29$ ($r^2 = 0{\cdot}96$, $P < 0{\cdot}001$) and $y = 1{\cdot}13x - 7{\cdot}32$ ($r^2 = 0{\cdot}96$, $P < 0{\cdot}001$); and in *D* (median latency, 302 ms): $y = 0{\cdot}55x - 4{\cdot}21$ ($r^2 = 0{\cdot}82$, $P < 0{\cdot}001$) and $y = 0{\cdot}41x - 1{\cdot}98$ ($r^2 = 0{\cdot}87$, $P < 0{\cdot}001$).

inactivation relationships of the two latency subgroups. For ipsiversive displacements (graphs *A* and *C*), a linear regression analysis of the relationship between horizontal amplitude (y) and horizontal retinal error (x) of short-latency movements (◇) gives the equations $y = 1{\cdot}18x - 22{\cdot}17$ and $y = 1{\cdot}11x - 9{\cdot}29$ for injections G1 and I2, respectively. For longer latency movements (◆), the resulting equations are $y = 1{\cdot}08x - 19{\cdot}62$ and $y = 1{\cdot}13x - 7{\cdot}32$ for injections G1 and I2, respectively. With regard to contraversive gaze shifts (graphs *B* and *D*), the linear regression analysis indicates a more pronounced hypometria of longer latency responses, as indicated by the decreased slopes in both relationships between horizontal retinal error and horizontal gaze amplitude (0·48 *versus* 0·65 for injection G1 and 0·41 *versus* 0·55 for injection I2), without any consistent change in the y-intercept (−1·56 *versus* −3·67 for injection G1 and −1·98 *versus* −4·21 for injection I2).

The consistency of these observations was statistically tested by comparing, between the short-latency and the longer latency groups, the slopes and y-intercepts of the regression lines computed in each experiment (Fig. 5). First of all, note the general decrease in the slope with weak modifications in y-intercept for contraversive movements (average changes from control values: $-0{\cdot}38 \pm 0{\cdot}05$ and $0{\cdot}91 \pm 1{\cdot}78$ for slope and y-intercept, respectively); conversely, y-intercept systematically varies in a consistent way (decreases or increases following inactivation of the left or the right cFN, respectively) with only minor increases in slope for ipsiversive movements (average changes from control values: $0{\cdot}16 \pm 0{\cdot}13$ and $8{\cdot}90 \pm 5{\cdot}37$ for slope and y-intercept, respectively). These features correspond to the pattern of gaze dysmetria that was previously reported for a smaller number of inactivation experiments (Goffart & Pélisson, 1994). We now ask, separately for each movement direction, whether these modifications are identical for the two latency subgroups. Regarding ipsiversive movements, the relationship between horizontal retinal error and horizontal gaze amplitude of longer latency responses is associated with a reduced slope for nine out of twelve experiments (Fig. 5*A*) and with a reduced y-intercept for seven experiments (Fig. 5*B*). However, a global analysis performed on all experiments pooled together (Student's paired t test) failed to reveal any statistically significant difference in slope (1·09 *versus* 1·14; t statistic for 11 degrees of freedom, $t_{11} = 1{\cdot}61$; $P > 0{\cdot}05$) as well as in y-intercept (−0·53 *versus* −0·59, $t_{11} = 0{\cdot}08$, $P > 0{\cdot}05$). Regarding contraversive movements (right-hand side of figure), a reduced slope is observed for eleven muscimol sessions (panel *C*) whereas the y-intercept decreases for seven experiments (panel *D*). The global analysis this time reveals a statistically significant difference in the slope (0·48 *versus* 0·58, Student's paired t test: $t_{11} = 2{\cdot}77$, $P < 0{\cdot}02$) but not in the intercept (−0·65 *versus* −0·38, $t_{11} = 0{\cdot}27$, $P > 0{\cdot}05$). To test whether this effect is specific of muscimol injections, we performed the same analysis for control responses of similar direction. A reduced slope is again observed in eight out of the twelve control sessions, but the global trend does not reach statistical significance ($t_{11} = 1{\cdot}76$, $P > 0{\cdot}05$; mean values, 0·90 *versus* 0·95).

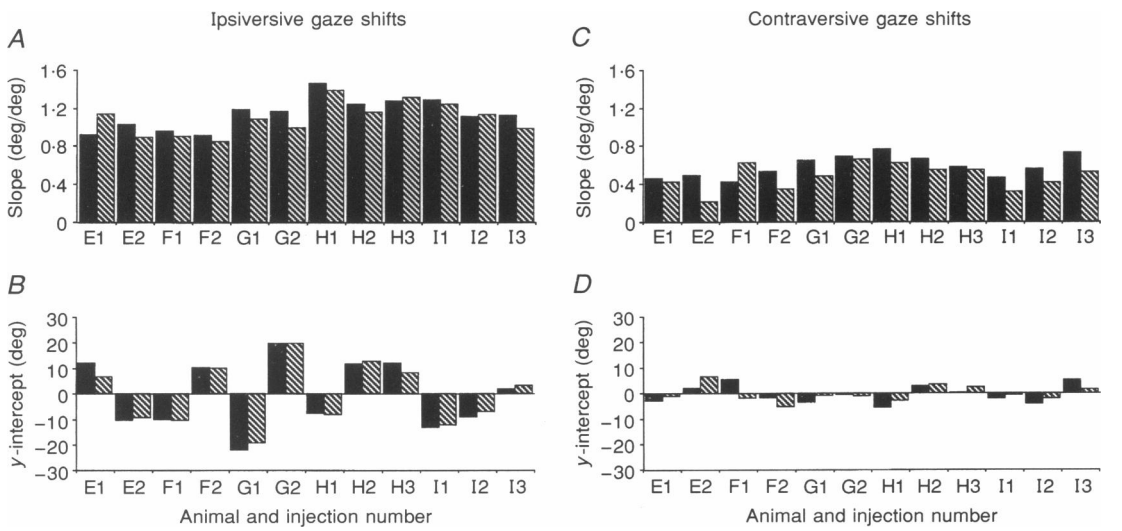

Figure 5. Latency and the relationship between horizontal retinal error and horizontal gaze amplitude after muscimol injection in the cFN

This figure reports the slope (*A* and *C*) and y-intercept (*B* and *D*) values of the regression lines fitting the relationships between horizontal retinal error and horizontal gaze amplitude of short-latency (■, latency < median) and longer latency (▨, latency > median) gaze shifts after muscimol injection in the cFN. Left and right panels correspond to ipsiversive and contraversive responses, respectively. Decreases or increases of y-intercept refer, respectively, to leftward or rightward shifts of gaze final position relative to the target. Muscimol injected in the left cFN (E2, F1, G1, H1, I1 and I2) or in the right cFN (E1, F2, G2, H2, H3 and I3).

This increased hypometria of contraversive gaze shifts for longer latencies was confirmed by the following analysis. For each experiment, we plotted the relationship between the gain and the latency of the movement. The gain is defined as the ratio of horizontal gaze shift amplitude to horizontal retinal error. Two examples of such relationships are presented in Fig. 6 for injections G1 (*A*) and I2 (*B*). For both experiments, average latency is longer after muscimol injection than before mainly because there are more longer latencies after injection. With respect to the gain parameter (ordinate), the pharmacological and control data do not overlap each other, corresponding to a primary effect of cFN inactivation decreasing the average gain. Note that gain decreases further as latency increases. This is reflected in the negative correlation between gain and latency in post-injection data (Pearson correlation coefficient $r = -0{\cdot}57$, $P < 0{\cdot}001$ for injection G1 and $r = -0{\cdot}53$, $P < 0{\cdot}001$ for injection I2). In the control session, either a negative ($r = -0{\cdot}09$ for cat I) or a positive ($r = 0{\cdot}09$ for cat G) non-significant trend can be noted. This correlation analysis has been applied to all control and muscimol experiments. A statistically significant ($P < 0{\cdot}05$) negative correlation has been found for nine out of the twelve pharmacological sessions and only for four of the control sessions.

Relation between gaze latency and retinal error or movement amplitude

From the data presented so far, it is demonstrated that the latency of movements directed away from an inactivated cFN is about twice as long as that of ipsiversive responses. With regard to the gaze inaccuracies after cFN inactivation, we have previously reported that the presentation of a target at a small retinal eccentricity in the contralesional hemifield often elicits an ipsiversive gaze shift, that is, a response that effectively moves gaze away from the target (Goffart & Pélisson, 1994). We examine now whether the latency characteristics of these misdirected movements are comparable with other ipsiversive movements or with responses to a similar retinal error. Figure 7 represents the latency of gaze shifts as a function of their amplitude for six pharmacological sessions that provided a significant number of misdirected movements (injections H1, H2, H3, G1, I1 and I2). To facilitate comparisons between inactivation experiments of the left cFN (H1, G1, I1 and I2) or right cFN (H2 and H3), ipsiversive movements are all represented with a positive gaze displacement and contraversive gaze displacements are negative, irrespective of their actual direction. The much larger amplitude range of ipsiversive movements with respect to contraversive ones reflects the characteristic pattern of ipsiversive hypermetria/contraversive hypometria. Note again the marked difference in the latency of gaze shifts according to their direction. In these plots, different symbols are used according to the retinal error that triggered the response: filled triangles represent movements towards a target presented in the ipsilesional hemifield (positive retinal error) whereas open triangles indicate responses elicited by presenting the target in the

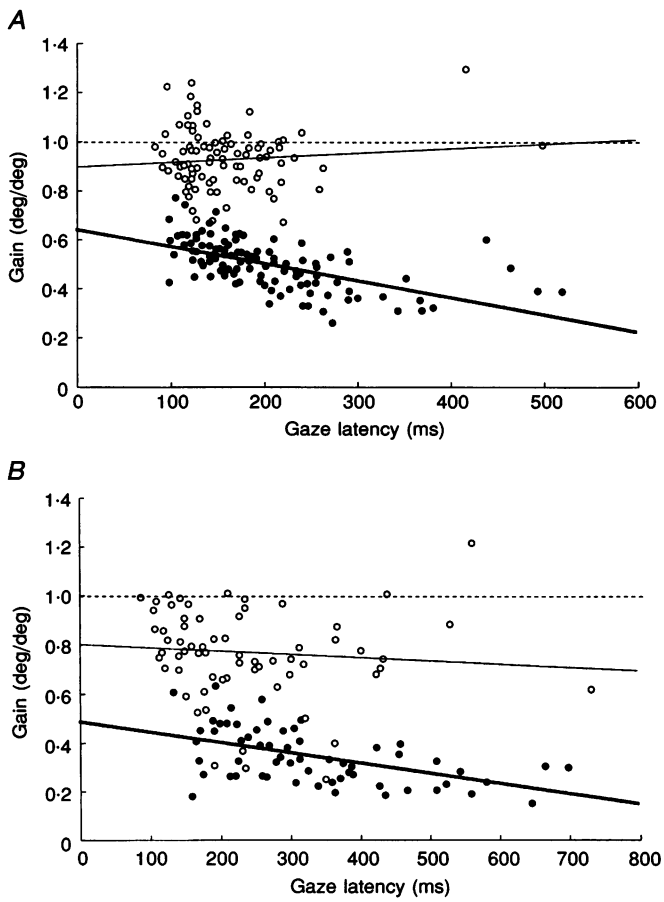

Figure 6. Latency and gain of contraversive gaze shifts after muscimol injection in the cFN

Relationship between gain (*y*-axis) and latency (*x*-axis) of contraversive responses recorded before (○) and after muscimol injection (●) in the left cFN of cat G (*A*) and I (*B*). Same data as those illustrated in Figs 2 and 4. Equations of the regression lines in *A*: $y = 0{\cdot}189 \times 10^{-3}x + 0{\cdot}89$ ($r^2 = 0{\cdot}008$, $P > 0{\cdot}05$) and $y = -0{\cdot}695 \times 10^{-3}x + 0{\cdot}64$ ($r^2 = 0{\cdot}33$, $P < 0{\cdot}001$) for control and muscimol data, respectively; in *B*: $y = -0{\cdot}134 \times 10^{-3}x + 0{\cdot}80$ ($r^2 = 0{\cdot}09$, $P > 0{\cdot}05$) and $y = -0{\cdot}423 \times 10^{-3}x + 0{\cdot}48$ ($r^2 = 0{\cdot}28$, $P < 0{\cdot}001$) for control and muscimol data, respectively.

contralesional hemifield (negative retinal error). Among this second category of gaze shifts, those corresponding to a small retinal error are in most cases directed towards the inactivated cFN (identified by open symbols situated to the right of each plot origin). It appears that the latency of these ipsiversive misdirected movements is quite variable and, on average, smaller than the latency of contraversive movements with a comparable retinal error. Indeed, for most injections, several misdirected gaze shifts have a latency very similar to that of the 'regular' ipsiversive responses (▲), whereas the remaining misdirected responses have an increased latency. Unfortunately, the large overlap between 'regular' ipsiversive and contraversive latencies does not permit us to statistically determine which of these two distributions best characterizes the latencies of misdirected gaze shifts.

From these plots, we also observe that the latency of small movements tends to increase. Other authors (Wyman & Steinman, 1973; Kalesnykas & Hallett, 1996) have reported a similar saccade latency peak and have attributed this peak to non-sensory factors such as an increased uncertainty in specifying the direction of small saccadic responses. We tested the hypothesis that non-retinal factors are responsible for the long latencies of small saccades by taking advantage of the disruption, induced by cFN inactivation, of the normal relationship between the visual stimulation

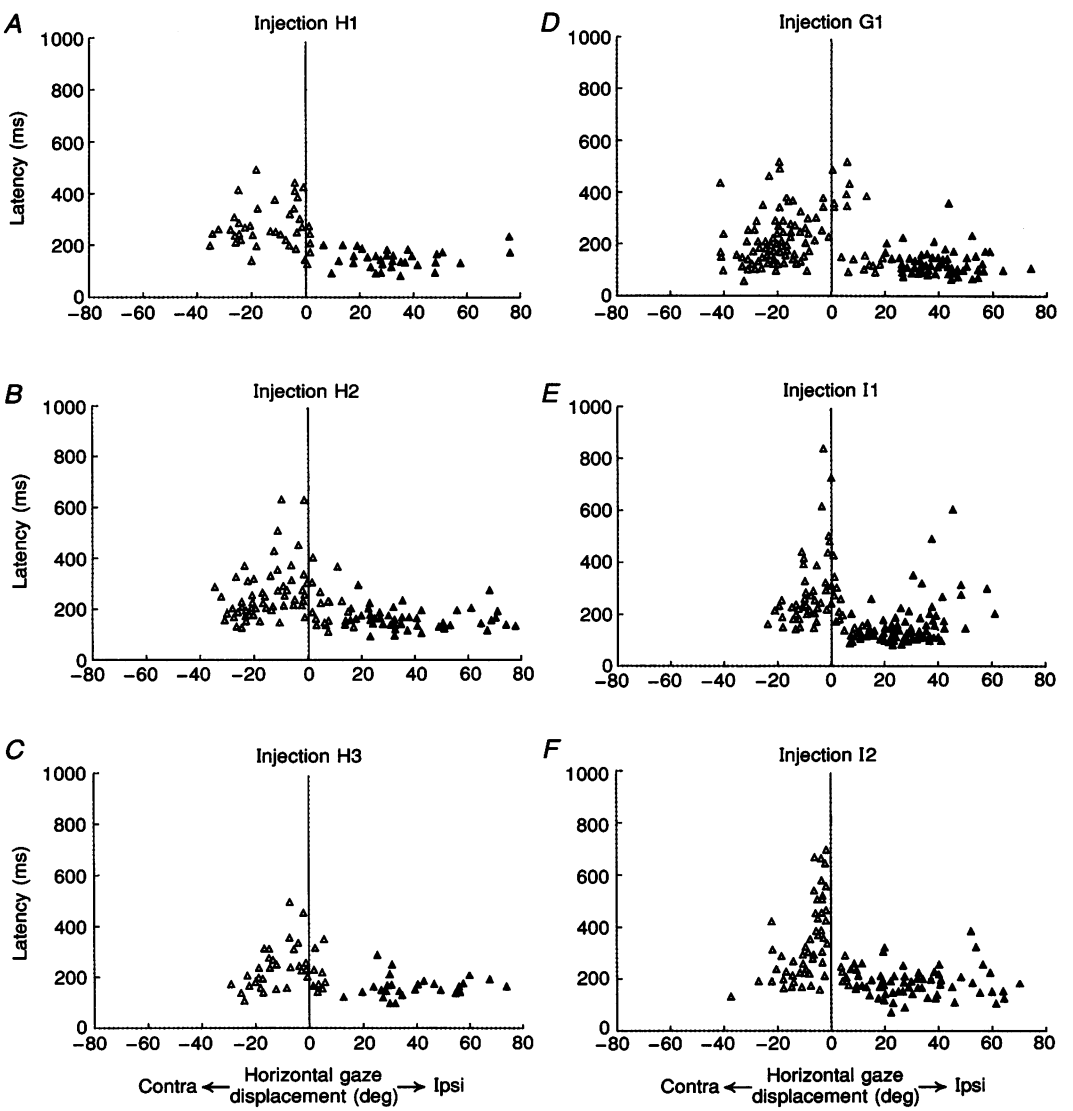

Figure 7. Latency *versus* horizontal gaze amplitude relationships in 6 pharmacological sessions (*A–F*)

Symbols: △, retinal error < 0; ▲, retinal error > 0. Each data point represents a gaze shift recorded after inactivation of left cFN (H1, G1, I1 and I2) or right cFN (H2 and H3). Data collected after inactivation of the left cFN were mirror-imaged to facilitate comparison with right cFN experiments: thus, for all experiments, ipsiversive (Ipsi) and contraversive (Contra) movements are represented with a positive and negative gaze displacement, respectively. Similarly, movements triggered by presenting the target in the ipsilesional or contralesional hemifield are depicted by ▲ or △, respectively.

and the associated gaze response. This disruption allowed us to examine whether the peak in gaze shift latency is better correlated to retinal error or to gaze displacement amplitude. In Fig. 8 data is replotted from three experiments (G1, I1 and I2) in which we collected the greatest number of small amplitude gaze shifts. Each data point represents the median latency (and interquartile ranges shown by error bars) of responses belonging either to the same amplitude bin or to the same retinal error bin. The three latency–amplitude curves (Fig. 8*A–C*) all show a characteristic asymmetrical shape following cFN inactivation: the curve is flat with reduced latencies for all ipsiversive responses except the smallest ones for which the curve rises steeply to culminate for the zero amplitude bin, then the latency progressively decreases as movement amplitude increases in the contraversive direction. The shape of latency–retinal error pharmacological curves (Fig. 8*D–F*) is quite similar to that of latency–amplitude curves, but there are two notable differences: the width of the latency–amplitude peak tends to be narrower (see experiments I1 and I2) and most interestingly, this peak is centred around the origin of the amplitude axis whereas that of the latency–retinal error is systematically displaced towards contralesional retinal errors. Note that the size of this shift in peak latency, that can be grossly estimated by visual inspection of the curves (20, 15 and 5 deg for experiments G1, I1 and I2,

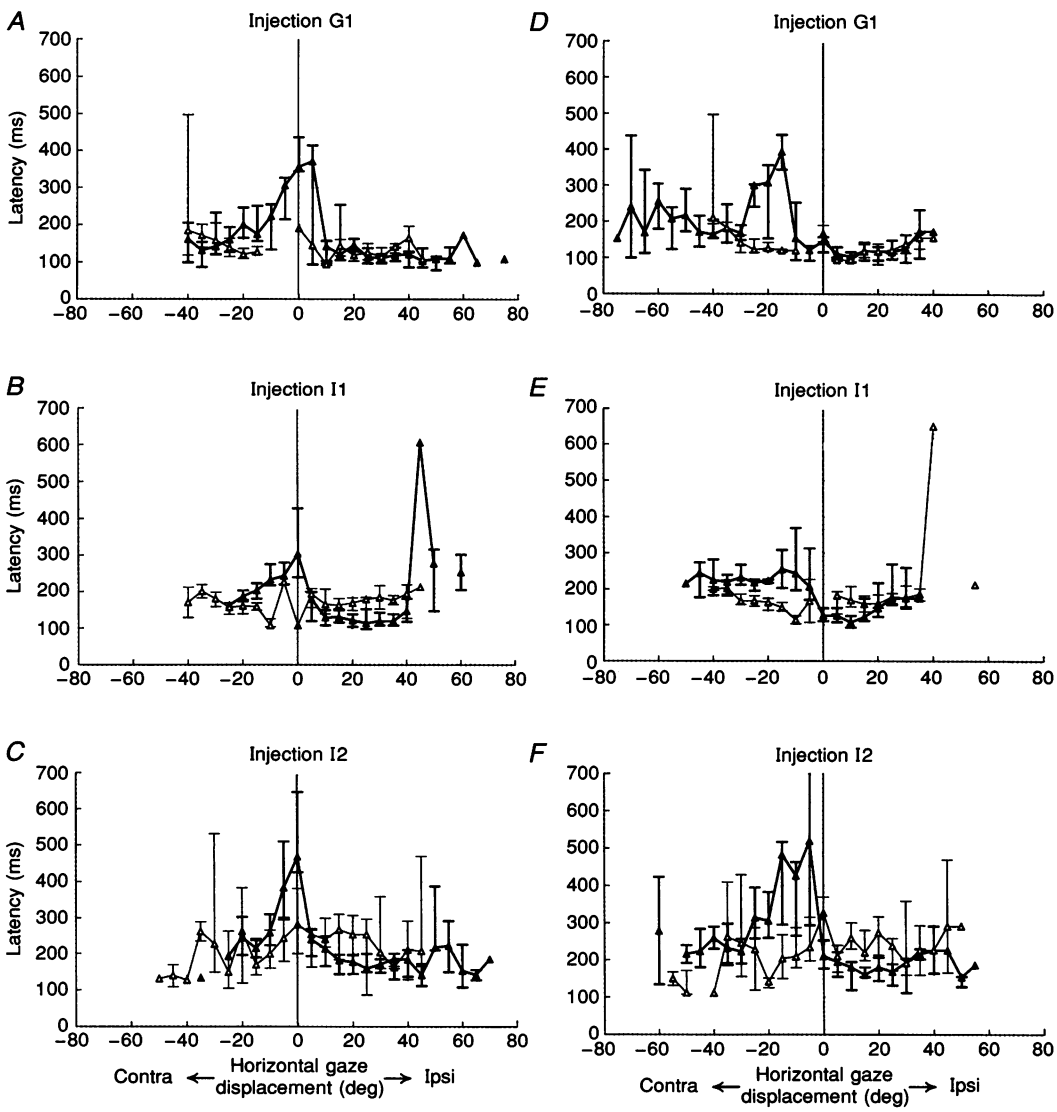

Figure 8. Latency/amplitude and latency/retinal error relationships for 3 experiments

Symbols: △, control; ▲, muscimol. Each data point represents the median latency (and 25/75% percentiles shown by vertical bars) of gaze shifts classified in intervals (5 deg bin width) of displacement amplitude (*A–C*) or retinal error (*D–F*). Symbols without percentile bar indicate single responses in the corresponding bins. For each panel, pharmacological and control data are shown superimposed. As in Fig. 7, gaze displacement and retinal error have been mirror-imaged and represent ipsiversive (Ipsi) and contraversive (Contra) directions as positive and negative values, respectively. Note the marked latency peak in the pharmacological sessions that corresponds to the smallest gaze displacements.

respectively), is similar to the inactivation-induced shift in the y-intercept of the relationship between horizontal retinal error and horizontal gaze amplitude (20·8, 12·9 and 8·0 deg for experiments G1, I1 and I2, respectively). Contrasting with the pharmacological data, no marked and consistent features can be noted in the control curves: we can only observe, in the two experiments that provided enough small responses (G1 and I2), a small peak in latency centred around the origin of both the latency–retinal error and the latency–amplitude relationships.

DISCUSSION

This study is to our knowledge the first report of consistent changes in the latency of visually triggered gaze shifts following restricted, unilateral inactivation of the cFN. Previous inactivation studies in the monkey failed to show any latency modification (Vilis & Hore, 1981; Robinson *et al.* 1993) either because of species differences or because of task differences. In our experiments, the animal produced co-ordinated eye and head movements to orient gaze towards the target while in the experiments cited above, monkeys made saccadic eye movements alone, as the head was restrained. Clinical studies do not report any change in saccadic latency in cerebellar patients tested in the head-fixed condition (Lewis & Zee, 1993; Gaymard, Rivaud, Amarenco & Pierrot-Deseilligny, 1994). On the other hand, a significant increase in the latency of head-unrestrained gaze shifts has been reported in patients with cerebellar ataxia (Shimizu, Naito & Yoshida, 1981). Further studies comparing head-free and head-fixed responses are required to determine whether freeing the head provides the optimal condition to observe changes in gaze saccade latency following cerebellar lesions. Another potentially important factor concerns visual target presentation. In the present study, we used a low-contrast visual stimulus that was suddenly unmasked from behind an occluder, yielding the only 'go' signal for the cat to trigger an orienting response. Instead, in experiments with monkeys, the visual target was a high contrast spot of light, and target onset was associated with the simultaneous extinction of the fixation point. Hence, it would be informative to investigate whether latency modifications after cFN dysfunction would change by manipulating target detectability or by dissociating the triggering signal from the target-related signal.

The data reported here show that muscimol injection in cFN leads to changes in latency that depend on movement direction with respect to the injected side. The latency of gaze shifts directed away from the inactivated cFN consistently increased and showed increased variability as compared to control responses whereas the latency of ipsiversive movements decreased. In addition, very similar modifications of head movement latency were observed, keeping the normal timing between eye and head components.

These different effects according to movement direction are reminiscent of the different kinds of gaze dysmetria observed for ipsiversive and contraversive gaze shifts. Indeed, as illustrated by previously published data (Goffart & Pélisson, 1994) and complemented by the present results, ipsiversive movements overshot the target essentially by a constant error, whereas contraversive gaze shifts undershot the target by an error that was proportional to the required displacement. Again, as for latency, these changes in gaze displacement affected eye and head components in parallel and did not modify the natural oculocephalic co-ordination (L. Goffart and D. Pélisson, unpublished data). Taken together, these latency and metric modifications suggest that the medio-posterior cerebellum contributes both to the processes that lead to the initiation of an orienting gaze response and to those that specify movement metrics. Now the question is to know whether these temporal and spatial modifications represent one common functional perturbation or two independent deficits.

Functional aspects of changes in gaze latency and of their relation to dysmetria

The inactivation of cFN induced by our muscimol injections should mimic that resulting from a sustained activation of Purkinje cell afferents. However, Ohtsuka & Noda (1991*a*) do not report any change in saccadic latency when a subthreshold electrical microstimulation is applied to the oculomotor vermis about 100 ms after target presentation. Hypometria of the subsequent saccades was the only reported consequence of such transient cFN inhibition. If the difference between this study and ours mainly resides in the temporal aspect of cFN inactivation, then it can be inferred that contraversive saccades are delayed only if cFN is inhibited during a critical period occurring within the first hundred milliseconds following target presentation. This possibility suggests a cerebellar involvement in the early processes that are initiated by a sensory event, such as the detection of a sensory stimulation. A cerebellar role in sensory detection processes would be compatible with a previously proposed activating effect exerted by the medio-posterior cerebellar areas on sensory processing at several mesencephalic, diencephalic and telencephalic levels (for review see Steriade, 1995). Along this line of thought, cFN inactivation could have disfacilitated mechanisms of visual target detection.

This hypothesis of a deficit in target detection proposed for contraversive gaze shifts needs to be conciliated with the associated decrease in accuracy, as illustrated by the negative correlation observed between latency and gain. This finding is rather surprising when one considers that a longer latency should provide the animal a longer period to estimate target location. A similar negative correlation between latency and gain of saccades has been found in some human subjects in a psychophysical experiment testing the effect of target duration on saccadic accuracy (Pernier, Jeannerod & Gerin, 1969). There are two major interpretations of the reduction in gaze accuracy with longer latencies after muscimol injection in the cFN. The first

assumes that movement initiation and metrics specification processes represent parallel and independent mechanisms, both triggered by the sensory stimulation. Changes in accuracy can be expected for longer latencies if cFN inactivation has increased the time to reach a 'decision' threshold for movement initiation (causing longer latency) (Carpenter & Williams, 1995) and in parallel weakened the mechanisms that contribute to sustain target-related signals in a short-term memory. In this perspective, the reference signal for the brainstem movement generators would correspond to the current state of this 'leaky' goal-related signal at the time a 'decision' signal closes the omnipause latch. The other interpretation postulates some sequential organisation between the triggering processes and those that specify movement metrics, with the 'when' mechanism being controlled by the 'where' mechanism. For example, if the target-related spatial information influences the growth of the 'decision' signal (Pernier *et al.* 1969), a single impairment of the former should lead to deficits in both movement metrics and movement initiation. It is not yet possible to favour one of these hypotheses and further cFN inactivation experiments are needed to test whether, by manipulating target detectability and saccade latency (using instructional stimuli), the medio-posterior areas of cerebellum are directly involved in target detection or in the 'decisional' processes that lead to the triggering of a response.

Contrasting with contraversive movements, the degree of hypermetria in ipsiversive gaze shifts was unrelated to latency. Thus, one can tentatively conclude that deficits in the metrics (Goffart & Pélisson, 1994) and in the initiation of these movements reveal independent influences of cFN upon these processes. Nevertheless, the strong inactivation-induced bias between the visual stimulation and the associated gaze response provided an opportunity to test whether the initiation of a gaze shift is controlled by pure sensory information or by signals closer to the motor output. The first clue is given by responses elicited by a target presented at a small retinal eccentricity in the contralesional hemifield but directed away from the target, towards the ipsilesional side. It appeared that about half of these misdirected movements had a latency comparable to that of other ipsiversive responses. The second clue comes from the observation that the latency of gaze shifts produced following cFN inactivation culminates for the smallest gaze displacements, and not for the smallest retinal errors, which is compatible with the view that saccadic initiation is dependent upon spatial information about the impending movement (desired displacement signal) coded in a motor, not sensory, frame of reference (Wyman & Steinman, 1973; Zambarbieri, Beltrami & Versino, 1995). This set of data thus constitute additional, although indirect, support for an influence, by processes specifying the metrics of an impending gaze shift, of the processes that initiate it. Another outcome of these results relates to the nature of cerebellar dysmetria. Indeed, the latency characteristics of misdirected gaze shifts indicate that the bias of ipsiversive responses end-point must have been introduced to the motor commands before the decision to trigger a response has been taken. This further supports our 'movement specification' hypothesis (Goffart & Pélisson, 1994).

Neurophysiological substrate

The data reported in this paper indicate that cFN activity normally inhibits the triggering of ipsiversive gaze shifts and facilitates the initiation of contraversive gaze shifts. As stated in the Introduction, these effects are compatible with previous anatomical and electrophysiological data. Regarding ipsiversive gaze shifts, inhibition of cFN may lead to a deactivation of omnipause neurons in the controlateral nucleus raphe pontis (Langer & Kaneko, 1984; Noda *et al.* 1990). Similarly, since caudal fastigial projection to the superior colliculus (SC) involves the rostral part of SC (e.g. Sugimoto *et al.* 1982; May *et al.* 1990; but see Roldan & Reinoso-Suarez, 1981), fixation neurons that have been described in this collicular area (Munoz *et al.* 1991; Munoz & Wurtz, 1993*a*) may also be deactivated. It is noteworthy that muscimol injection in this collicular 'fixation' zone in the monkey also reduces saccade latency (Munoz & Wurtz, 1993*b*). However, no saccadic dysmetria was reported, suggesting that deficits of gaze shifts directed towards an inactivated cFN cannot be reduced to a deafferentation of rostral SC. The reduced latency of ipsiversive gaze saccades is also compatible with the behavioural consequences of a transient cFN inhibition induced by applying electrical microstimulation to lobules VI–VII (oculomotor vermis). Indeed, such microstimulations trigger saccades directed towards the stimulated side (Fujikado & Noda, 1987) or, when delivered during the latency period in a visually triggered saccade task, cause a premature triggering of ipsilateral saccades (Noda *et al.* 1990).

A facilitation exerted by cFN output on the triggering of contraversive gaze shifts is compatible with both cell recording and stimulation experiments. Indeed, electrophysiological studies report a pre-saccadic burst before contraversive saccades (Ohtsuka & Noda, 1991*b*; Fuchs *et al.* 1993; Gruart & Delgado-Garcia, 1994) and electrical microstimulation of the cFN evokes a saccadic eye movement away from the stimulated side (Cohen *et al.* 1965; Noda *et al.* 1988). Projections of the cFN to the contralateral reticular formation (Fuchs *et al.* 1993) and to the superior colliculus may both be involved in initiation of contraversive gaze shifts. Identifying which neurons within these structures are involved will help understand whether cFN controls the triggering and the metrics of contraversive gaze shifts in a parallel or in a sequential way.

Concluding remarks

In conclusion, the observed effects of fastigial inactivation on saccade latency cannot be explained only in terms of movement execution, but instead provide further support to the hypothesis of a critical role of cFN during the preparation of gaze shifts (Goffart & Pélisson, 1994). In addition, changes in head latency paralleling those of gaze

latency suggest that the underlying pharmacologically induced modifications are located upstream from the level(s) where the timing of ocular and cephalic contribution to the gaze shift is controlled. Although it does not lead to an unequivocal interpretation, the worsening of contraversive movements hypometria with latency suggests that under normal circumstances, the medio-posterior cerebellum could participate in stabilizing spatial information necessary to the preparation of an accurate gaze saccade.

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